Volume Management with Kidney Replacement Therapy in the Critically Ill Patient

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Abstract

While the administration of intravenous fluids remains an important treatment, the negative consequences of subsequent fluid overload have raised questions about when and how clinicians should pursue avenues of fluid removal. Decisions regarding fluid removal during critical illness are complex even for patients with preserved kidney function. This article seeks to apply general concepts of fluid management to the care of patients who also require KRT. Because optimal fluid management for any specific patient is likely to change over the course of critical illness, conceptual models using phases of care have been developed. In this review, we will examine the implications of one such model on the use of ultrafiltration during KRT for volume removal in distributive shock. This will also provide a useful lens to re-examine published data of KRT during critical illness. We will highlight recent prospective trials of KRT as well as recent retrospective studies examining ultrafiltration rate and mortality, review the results, and discuss applications and shortcomings of these studies. We also emphasize that current data and techniques suggest that optimal guidelines will not consist of recommendations for or against absolute fluid removal rates but will instead require the development of dynamic protocols involving frequent cycles of reassessment and adjustment of net fluid removal goals. If optimal fluid management is dynamic, then frequent assessment of fluid responsiveness, fluid toxicity, and tolerance of fluid removal will be needed. Innovations in our ability to assess these parameters may improve our management of ultrafiltration in the future.

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Introduction

KRT plays a fundamental role in the management of fluid balance in the critically ill. However, management is complex and often particularly challenging in the setting of distributive shock. Intravenous fluids are a cornerstone of resuscitation.[1,2] However, the hemodynamic effect of volume expansion is often short-lived, and many clinicians continue to reflexively infuse fluids in absence of evidence of fluid responsiveness.[2,3] Critical illness itself contributes to retention of fluids through multiple insults to the integrity of the vascular endothelium.[4] The resultant fluid overload has increasingly been recognized as a complication of critical illness and is associated with higher morbidity and mortality.[4–9] However, studies that have examined this relationship are highly susceptible to confounding even when adjusting for severity of illness. Given that many patients who develop fluid overload also remain hypotensive, decisions regarding optimal fluid removal remain complex.[10]

In the context of such uncertainty, what paradigms should we use to guide decisions regarding fluid removal using KRT in the intensive care unit (ICU)? In this review, we describe KRT fluid management models that are broadly applicable to most ICU patients (although management of patients with primarily cardiogenic shock is outside the scope of this review).

Phases of Fluid Management

A working group of nephrologists and intensivists in the Acute Dialysis Quality Initiative proposed a conceptual framework to guide the administration and removal of fluid during critical illness.[11] The model consists of four phases: Resuscitation, Optimization, Stabilization, and De-escalation (ROS-D).[11] The ROS-D paradigm seeks to move beyond labels of conservative versus liberal fluid management and recognizes that the optimal strategy during one phase of illness may be unhelpful or even dangerous during another.[12,13] This context-dependent approach has some important implications in the management of patients receiving KRT (Figure 1).

During the rescue phase, a large amount of intravenous fluid is given immediately after the recognition of distributive or hypovolemic shock. Fluid is typically given rapidly, often according to a weight-based protocol such as the Surviving Sepsis Campaign recommendation of administering 30 cc/kg of isotonic fluid within the first 3 hours of resuscitation.[14] The goal is to give fluid quickly rather than to give incremental test doses. Fluid removal using KRT is unlikely to have a role in this phase.

In the optimization phase, intravenous fluid is given more judiciously. Volume management is guided by evidence of improved tissue perfusion after fluid challenges. While fluid removal during a volume challenge would clearly be counterproductive, these fluid challenges may contribute to fluid accumulation that will eventually need to be addressed.

In the stabilization phase, tissue perfusion is no longer fluid-responsive, so a net positive state is not

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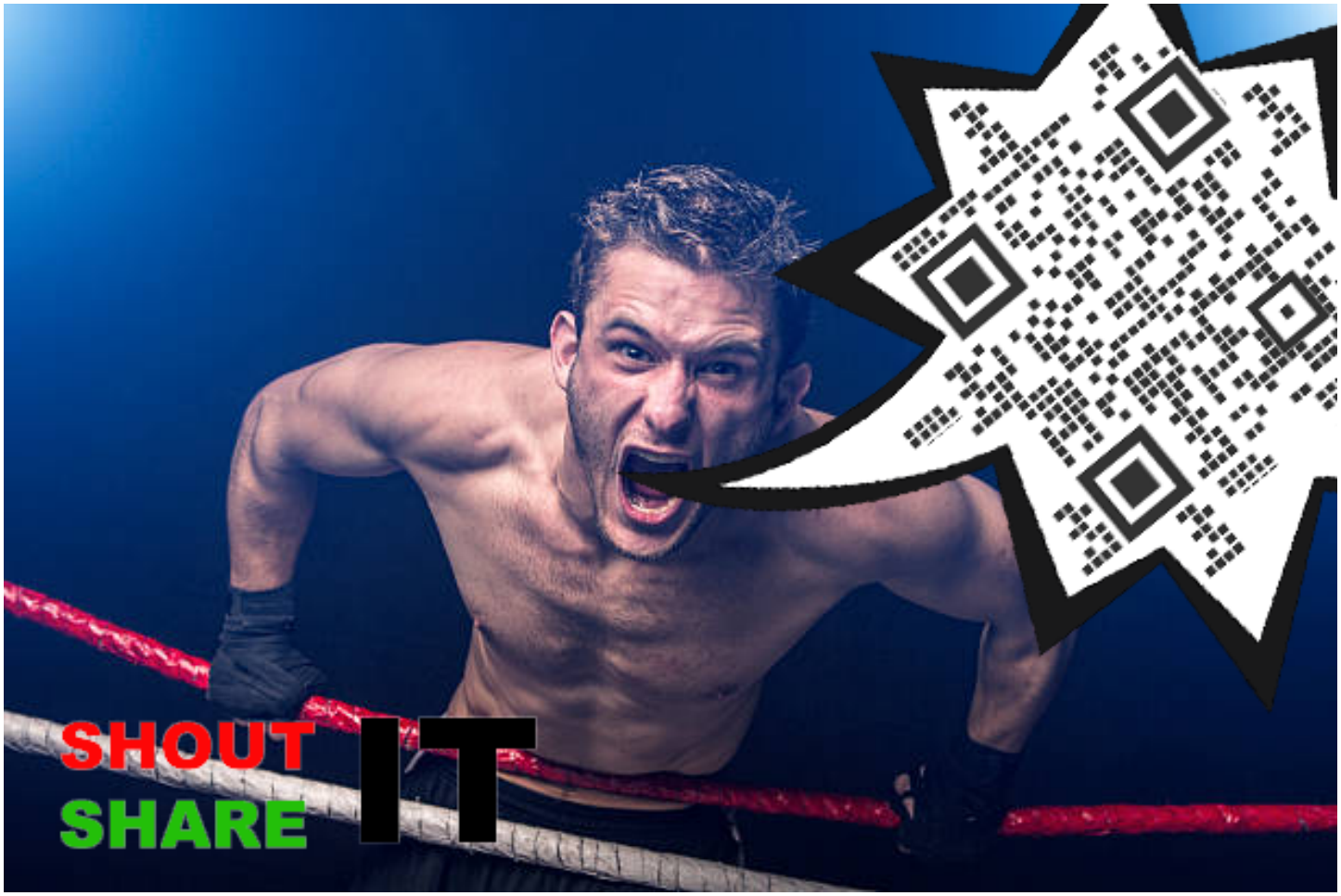
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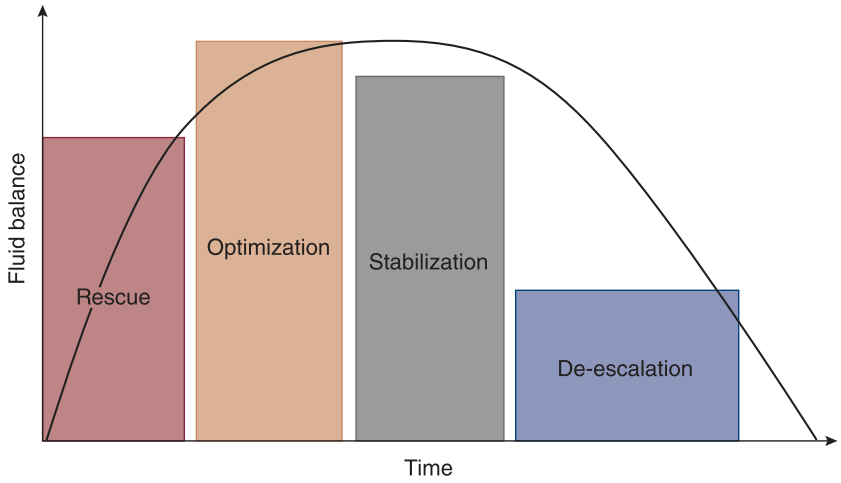

Phase	(R) Rescue	(O) Optimization	(S) Stabilization	(D) De-escalation
Also known as	Salvage or resuscitation			De-resuscitation or evacuation
Features	Often early in recognition of shock	Often remain hemodynamically unstable	Organ perfusion and/or cardiac output not augmented by fluid administration, but vulnerable to net fluid removal	Improved hemodynamic stability sufficient to tolerate fluid removal
Fluid strategy	Fluid administration with high priority given to rapid fluid delivery	Fluid administration titrated to hemodynamic response and/or measures of organ perfusion	Attempt to keep fluid input and fluid output approximately equal	Fluid removal to reverse the consequences of fluid overload
Potential metrics	• Weight-based protocol • Completed within 3h of recognition of distributive shock	• Assess mean arterial blood pressure • Assess cardiac output (or surrogate markers) • Assess tissue perfusion	• Assess anticipated input from all sources (medications, nutrition, electrolyte repletion) • Assess output (urine, drains, enteral, insensible losses) • Monitor for development of fluid overload	• Resolution of peripheral and pulmonary edema (physical exam, point-of-care ultrasound, chest x-ray, need for mechanical ventilation) • Assess tissue perfusion during net fluid removal
Considerations for fluid removal strategy	• Avoid fluid removal	• Minimize fluid removal unless receiving significant amounts of non-resuscitative fluid	• Fluid removal to prevent accumulation of non-resuscitative fluid • Assess optimal KRT modality to achieve goals	• Fluid removal guided by severity of volume overload • Assess optimal KRT modality to achieve goals

Figure 1. Summary of the different phases of resuscitation and patient volume status. Included are clinical features of each phase, general fluid strategy, some potential metrics to guide fluid delivery, and considerations for fluid removal. Image adapted from ADQI (2013).

desirable. However, significant net fluid removal should also be avoided because patients in this phase are not sufficiently hemodynamically stable to tolerate it. A net even goal is therefore typical. While this goal might seem simple, it is often difficult to achieve. Even if no resuscitative fluid is given, ICU patients frequently receive significant amounts of fluid through medications and nutrition. In one large single-center cohort of ICU patients, medications and nutrition accounted for 66% of total fluid intake.[15] Patients in the stabilization phase may intermittently decompensate, leading to further intravenous fluid administration. As a result, fluid removal using KRT may become critical during stabilization to prevent ever-worsening venous congestion. In patients with large amounts of daily fluid intake, more resource-intensive KRT modalities such as frequent intermittent treatments, prolonged intermittent therapy,[16] or continuous KRT (CKRT) may be beneficial in achieving volume management goals.

Finally, during the de-escalation phase (also known as deresuscitation), hemodynamics have improved sufficiently to tolerate the removal of fluid that has accumulated during earlier phases. The goal of this phase is to return the patient to a state of minimized tissue edema, a process often referred to as decongestion. KRT becomes essential for patients who cannot be decongested by other means. While patients in this phase have improved sufficiently to tolerate net fluid removal, they have not necessarily returned to their baseline hemodynamic state. A

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potential pitfall in such patients is the temptation to transition away from resource-intensive therapies too early and thereby undermine the achievement of decongestion.[17] In short, clinicians may have to choose between de-escalating fluid congestion versus de-escalating resource-intensive KRT modalities.

Fluid Responsiveness

Assessing fluid responsiveness is critical to fluid management paradigms such as ROS-D.[18,19] All existing methods of gauging fluid responsiveness are imperfect. Fluid responsiveness is often defined as a 10%–15% increase in cardiac output after intravenous fluid administration. Classically, cardiac output is measured through pulmonary artery catheterization using thermodilution or the Fick principle using mixed venous oxygen saturation. However, catheter-based methods are invasive and can serve as a portal for infection. Point-of-care ultrasound provides a noninvasive technique to estimate stroke volume by measuring aortic valve area and flow[20] but requires significant expertise. As a result, in clinical settings, an increase in systolic BP, pulse pressure, or mean arterial pressure (MAP) immediately after fluid administration is often used as a metric fluid of responsiveness instead of change in cardiac output. However, the correlation between these metrics and cardiac output after fluid challenge has been inconsistent across studies.[21–23] Finding better predictors of fluid responsiveness has been the subject of several recent reviews,[24] including from the *CJASN* Critical Care Nephrology and Acute Kidney Injury Series.[25] Unfortunately, many of these metrics require invasive measurements or ultrasound expertise or have only been validated in a subset of patients undergoing mechanical ventilation with specific respiratory system mechanics—typically deep sedation and/or relatively normal lung compliance.[4,26–28]

Despite these limitations, assessing fluid status and responsiveness through a multimodal approach means remains a core part of the everyday care of critically ill patients.[24,25] While it may be challenging to define the management phase of individual patients with certainty, fluid paradigms such as ROS-D may nevertheless provide a useful lens in evaluating current studies of KRT and their ability to inform optimal fluid removal in the critically ill.

Limitations of Trials of KRT Initiation

Several randomized clinical trials (RCTs) have examined the timing of initiation of KRT at the onset of critical illness (Table 1).[29–37] However, such studies may not be ideal to answer questions about fluid removal. By design, these trials focused on initiation of KRT shortly after the development of AKI. In the critical care setting, the first 24 hours of AKI development often coincides with hemodynamic instability. Trials examining early initiation of KRT may therefore be likely to include patients in phases of management where volume removal is not yet desirable. While this hypothesis is impossible to confirm, it is notable that across all trials where the cause of KRT initiation was reported, only a minority of participants had KRT initiated for volume management. In addition, in all but one trial (Standard versus Accelerated Initiation of Renal-Replacement Therapy in Acute Kidney Injury [STARRT-AKI]), there was no significant difference in fluid balance reported between the randomized arms. In fact, supplemental data from the IDEAL-ICU trial showed that participants in the early arm had a median daily fluid removal by KRT of 0 ml for each of the 7 days after randomization. An exception was the STARRT-AKI trial, where a prespecified secondary analysis of participants with fluid balance data collected showed a 1.1 L ($P = 0.03$) difference between the two groups at 14 days.[38] There was no significant difference in fluid balance for the subgroup that remained in the ICU at 14 days.

Limitations of Trials of Intermittent versus Continuous or Prolonged KRT

RCTs of intermittent KRT versus either CKRT or prolonged intermittent therapy have found no difference in all-cause mortality.[39] However, the protocols of these trials were not designed to create differences in fluid balance between the treatment arms. In fact, only five of ten trials comparing CKRT with intermittent KRT even quantified net fluid balance.[40–49] Of these five, four showed no between-group differences,[42–44,46] and one reported greater net negative fluid balance in the CKRT group at 72 hours but no fluid balance data after that.[40] A study by Mehta *et al.* did not report net fluid balance but did note that 28.8% of intermittent KRT treatments fell short of ultrafiltration goals, compared with just 9% of treatments in the CKRT arm.[41]

In the meantime, a lack of evidence is not evidence of lack of effect. Although useful trial data are absent, enhanced fluid removal using CKRT as compared with intermittent KRT is both physiologically reasonable and has some support, albeit limited, from cross-sectional data.[50]

Optimizing Randomized Trial Design

In designing trials of fluid management in patients not requiring KRT, intensivists have suggested trialing conservative fluid management or goal-directed fluid removal during the stabilization and de-escalation phases, during which fluid removal may be both feasible and impactful.[13,51] Future trials of fluid removal using KRT might also focus on such later phases of management rather than the period immediately after AKI.

In addition, trials of volume management using diuretics—such as one in patients with acute respiratory distress syndrome[52]—used detailed protocols to achieve differences in net volume status between treatment arms. Future trials of volume management with KRT will likely need such protocols to guide the initiation, management, and discontinuation of therapy. Given the uncertainty around these aspects of study design, pilot studies may be needed before trials can be attempted on a larger scale.

Mixed Results from Observational Studies of Ultrafiltration Rate

If currently available RCTs are not sufficient to guide optimal KRT fluid strategies, what about cohort data? Four recent retrospective studies examined whether the rate of ultrafiltration in critically ill patients receiving KRT is associated with mortality (Table 2).[53–56] Because KRT requires some administration of intravenous fluid (to prime the circuit, rinse back blood, and replace fluid if hemofiltration is used), these studies refer to fluid removal

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Table 1. Randomized controlled trials investigating the timing of initiation of KRT

Trial	Patients	KRT Modality	Indication for Trial Enrollment	Criteria for Delayed KRT Initiation	Mortality Difference		Median Time from Randomization to KRT		KRT Initiated for Volume (%)	Cumulative Fluid Balance during Trial Period
					Follow-up (d)	Benefit	Early KRT	Late KRT	Late KRT	
HEROICS[29]	224	CVVH	High-dose catecholamine infusion after cardiac surgery or extracorporeal membrane oxygenation requirement	1. AKIN stage III AKI 2. BUN >100 mg/dl 3. Life-threatening hyperkalemia	30	No	Unk	Unk	0	Unknown
ELAIN[30]	231	CVVHDF	1. KDIGO stage II AKI 2. NGAL >150 ng/ml 3. Severe sepsis 4. Use of vasopressors 5. PaO_2:FiO_2 <300 mm Hg 6. Fluid balance >10% of ABW	1. BUN >100 mg/dl 2. Potassium >6 mEq/L w/ EKG changes 3. Magnesium >4 mmol/L 4. Urine output <200 ml/12 h 5. Organ edema resistant to loop diuresis	90	Yes	6 h	25.5 h	Unk	No significant difference in cumulative fluid balance between groups 3 d after randomization
AKIKI[31]	619	Any	KDIGO stage III AKI and either VDRF or vasopressor use	1. Oliguria >72 h after randomization 2. BUN >112 mg/dl 3. Potassium >5.5 mmol/L despite treatment 4. pH <7.15 5. Pulmonary edema due to fluid overload, refractory to diuretics, requiring >5 L/min of supplemental oxygen or >50% FiO_2	28	No	2 h	57 h	6	Unknown
IDEAL-ICU[37]	488	Any	RIFLE stage F AKI	1. Potassium >6.5 mmol/L 2. pH <7.15 3. Pulmonary edema refractory to diuretics	90	No	7.6 h	51.5 h	2	No significant difference in cumulative fluid balance between groups 7 d after randomization
FST[32]	118	CVVH	Negative furosemide stress test	1. BUN >100 mg/dl 2. Potassium >6 mmol/L 3. Serum bicarbonate <12 mmol/L 4. pH <7.15 5. Pulmonary edema or PaO_2/FiO_2 <200 mm Hg	28	No	2 h	21 h	Unk	No significant difference in cumulative fluid balance between groups 7 d after randomization
Srisawat *et al.* 2018[35]	40	CKRT	pNGAL ≥500 ng/ml	1. pH <7.20 or serum bicarbonate <15 mEq/L 2. Severe peripheral edema or pulmonary edema refractory to diuretics 3. Potassium >6.2 mEq/L 4. Oliguria 5. BUN >60 mg/dl	28	No	1 d	3 d	25	No significant difference in cumulative fluid balance between groups 28 d after randomization
HYPERDIA[36]	35	CKRT	Postcardiac arrest	Standard indication for KRT	7	No	Unk	Unk	Unk	Unknown

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Table 1. (Continued)

Trial	Patients	KRT Modality	Indication for Trial Enrollment	Criteria for Delayed KRT Initiation	Mortality Difference		Median Time from Randomization to KRT		KRT Initiated for Volume (%)	Cumulative Fluid Balance during Trial Period
					Follow-up (d)	Benefit	Early KRT	Late KRT	Late KRT	
STARRT-AKI[33]	3019	Any	KDIGO stage II AKI or urine output <6 ml/kg for 12 h	1. Potassium >6.0 mmol/L 2. pH ≤7.20 3. Serum bicarbonate ≤12 mmol/L 4. Fluid overload with PaO_2/FiO_2 ≤200 mm Hg 5. Persistent AKI 72 h after randomization	90	No	6.1 h	31.1 h	43.6	1.1 L difference in fluid balance at 14 d ($P = 0.03$)
AKIKI-2[34]	278	Any	KDIGO stage III AKI and either ventilatory-dependent respiratory failure or vasopressor use with 1. Oligoanuria >72 h or 2. BUN >112 mg/dl	1. BUN >140 mg/dl 2. Potassium >5.5 mmol/L despite treatment 3. pH <7.15 4. Pulmonary edema due to fluid overload, refractory to diuretics, requiring >5 L/min of supplemental oxygen or >50% FiO_2	28	No	3 h	33 h	10	No significant difference in cumulative fluid balance between groups either 2 or 7 d after randomization

HEROICS, Hemofiltration to Rescue Severe Shock following Cardiac Surgery; CVVH, continuous venovenous hemofiltration; AKIN, Acute Kidney Injury Network; Unk, unknown; ELAIN, Early versus Late Initiation of Renal Replacement Therapy in Critically Ill Patients with Acute Kidney Injury; CVVHDF, continuous venovenous hemodiafiltration; KDIGO, Kidney Disease Improving Global Outcomes; NGAL, neutrophil gelatinase–associated lipocalin; PaO_2, partial pressure of oxygen in arterial blood; FiO_2, fraction of inspired oxygen; ABW, admission body weight; EKG, electrocardiogram; AKIKI, Artificial Kidney Initiation in Kidney Injury; VDRF, ventilator-dependent respiratory failure; RIFLE, Risk, Injury, Failure, Loss, and End-stage renal failure; FST, furosemide stress test; CKRT, continuous KRT; pNGAL, plasma neutrophil gelatinase–associated lipocalin; STARRT-AKI, Standard versus Accelerated Initiation of Renal-Replacement Therapy in Acute Kidney Injury.

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Table 2. Comparison of studies examining ultrafiltration rate and mortality

Study	Population	Pre-KRT Fluid Status	KRT Modality	Exposure	Outcome/Results	Notable Features
Murugan *et al.* (2018)[53,a]	Retrospective cohort Single-center Medical and surgical ICU Jul 2000–Oct 2008 Pittsburgh, USA *N*=1075 AKI only	Fluid overload ≥5% body weight on admission	Intermittent HD and CKRT - CVVHDF - CVVHD - CVVH - SCUF	UF intensity - Low (≤20 ml/kg per day) - Moderate (20–25 ml/kg per day) - High (>25 ml/kg per day) Subgroup CKRT only - Low (<0.5 ml/kg per hour) - Moderate (0.1–1.0 ml/kg per hour) - High (>1.0 ml/kg per hour)	High-intensity UF (versus low-intensity) associated with improved 1-yr survival No difference between moderate- versus low-intensity groups Secondary outcomes - Hospital LOS - In-hospital mortality - Kidney recovery	Sensitivity analyses - Explored alternative UF thresholds - Propensity score matching - Quantitative bias analysis Demographic differences - Liver disease more in low-intensity group - Lower BP in low-intensity group - Higher vasopressor dose in low-intensity group - Higher KDIGO stage in high-intensity group
Tehranian *et al.* (2019)[54,a]	Retrospective cohort Single-center Medical and surgical ICU Dec 2006–Nov 2015 *N*=1398 Minnesota, USA AKI only	No criteria Subset analysis of fluid overload ≥10% body weight on admission	CKRT (CVVH)	UF intensity - Low (<35 ml/kg per day) - High (≥35 ml/kg per day)	High-intensity UF (versus low-intensity) associated with improved 30-d survival Secondary outcomes - Hospital LOS - In-hospital mortality - MAKE90 - Kidney recovery - 90-d mortality	Sensitivity analyses - Explored alternative UF thresholds - Subgroup analyses Demographic differences - More early hypotension in low-intensity group - More mechanical ventilation in high-intensity group
Murugan *et al.* (2019)[55,b]	Secondary analysis (RENAL trial) Multicenter Dec 2005–Nov 2008 Australia/New Zealand *N*=1434 AKI only	No criteria	CKRT (CVVHDF)	UF rate - Low (<1.01 ml/kg per hour) - Moderate (1.01–1.75 ml/kg per hour) - High (>1.75 ml/kg per hour)	High UF rate (versus low UF rate) associated with higher 90-d mortality Lowest mortality in the moderate UF rate group Higher complications in high UF rate group (not significant after adjustment for clearance and duration of CKRT)	Sensitivity analyses - Explored alternative UF thresholds - Propensity score matching - Varied time intervals - Subgroup analyses Demographic differences - Longer ICU length of stay prior to randomization in high UF rate group - More mechanical ventilation in high UF rate group - More CKRT initiation for severe organ edema due to kidney disease in high UF rate group

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Table 2. (Continued)

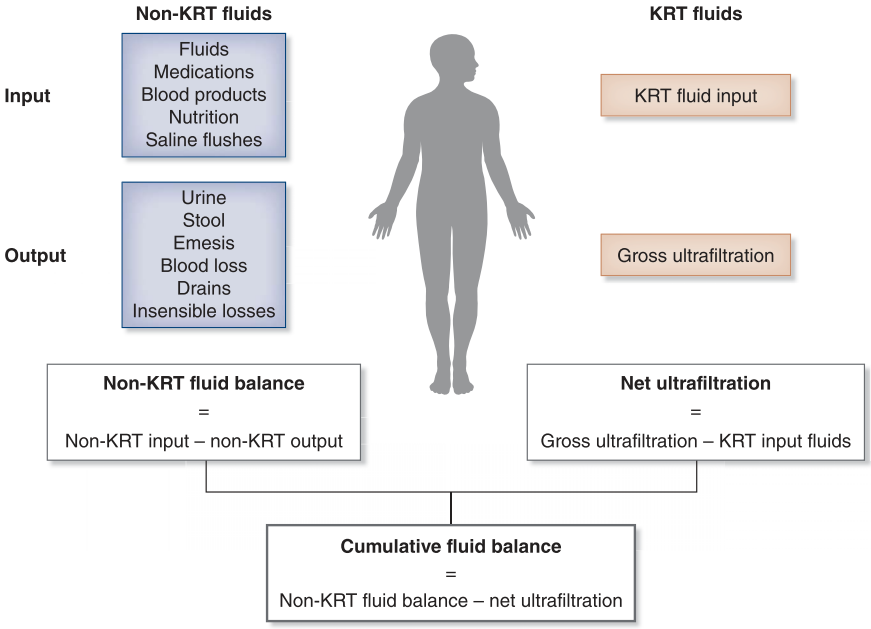
Study	Population	Pre-KRT Fluid Status	KRT Modality	Exposure	Outcome/Results	Notable Features
Naorungroj *et al.* (2021)[56,b]	Retrospective cohort Single-center Medical and surgical ICU 2016–2018 Australia *N*=347 AKI and chronic kidney failure	No criteria	CRKT - CVVHDF - CVVH	UF rate (in first 48 h) - Low (<1.01 ml/kg per hour) - Moderate (1.01–1.75 ml/kg per hour) - High (>1.75 ml/kg per hour)	High UF rate (versus low UF rate) associated with higher 28-d mortality	Sensitivity analyses - Subgroup analyses - Varied time of mortality assessment Demographic differences - Higher vasopressor use in low UF rate group - Longer duration of KRT in high UF rate group

This table provides a summary of the studies examining ultrafiltration and mortality in a critical care setting, with comparisons of study population, inclusion criteria, KRT modality, definition of net UF groups, outcomes, and other notable features. Note that while the studies refer to a net UF to account for the administration of intravenous fluids needed to complete KRT (in the case of these studies, this consisted of replacement fluid during hemofiltration) to avoid confusion, all fluid removal achieved using KRT is referred to simply as UF. ICU, intensive care unit; HD, hemodialysis; CKRT, continuous KRT; CVVHDF, continuous venovenous hemodiafiltration; CVVHD, continuous venovenous hemodialysis; CVVH, continuous venovenous hemofiltration; SCUF, slow continuous ultrafiltration; UF, ultrafiltration; LOS, length of stay; KDIGO, Kidney Disease Improving Global Outcomes; RENAL, Randomized Evaluation of Normal versus Augmented Level (RENAL) Replacement Therapy Study.

[a]The two studies that found an association between higher ultrafiltration rate and lower mortality.

[b]The two studies that found an association between higher ultrafiltration rate and higher mortality.

as net ultrafiltration. However, the term net ultrafiltration can be misleading because it can be mistaken for net fluid balance. Figure 2 serves to illustrate the potential for confusion regarding metrics such as net ultrafiltration. As a result, except in Figure 2, we will refer to net ultrafiltration as simply ultrafiltration. Ultrafiltration intensity is typically obtained by dividing ultrafiltration by admission weight and by unit of time.[53] For patients receiving only CKRT, the



Illustrative example in a 100-kg patient	Kidney replacement therapy (KRT) modality			
	Intermittent	Prolonged or extended	Continuous	
			CVVHD	CVVH
KRT duration[a]	4 h	10 h	24 h	24 h
Gross ultrafiltration[b]	2.5 L	2.5 L	2 L	50 L
KRT fluid input[c]	0.5 L	0.5 L	0 L	48 L
Net ultrafiltration[d]	2 L/24 h	2 L/24 h	2 L/24 h	2 L/24 h
Net UF intensity of KRT[e]	20 mL/kg/day	20 mL/kg/day	20 mL/kg/day	20 mL/kg/day
Maximum hourly net UF rate	625 mL/h	250 mL/h	83 mL/h	83 mL/h
Net UF intensity if only CKRT[f]	n/a	n/a	0.83 mL/kg/h	0.83 mL/kg/h
Example with **low** daily input (non-KRT)				
Input (non-KRT)	1 L	1 L	1 L	1 L
Output (non-KRT)	0.5 L	0.5 L	0.5 L	0.5 L
Net UF (KRT)	2 L	2 L	2 L	2 L
Net fluid balance	– 1.5 L/24 h	– 1.5 L/24 h	– 1.5 L/24 h	– 1.5 L/24 h
Example with **high** daily input (non-KRT)				
Input (non-KRT)	5 L	5 L	5 L	5 L
Output (non-KRT)	0.5 L	0.5 L	0.5 L	0.5 L
Net UF (KRT)	2 L	2 L	2 L	2 L
Net fluid balance	+ 2.5 L/24 h	+ 2.5 L/24 h	+ 2.5 L/24 h	+ 2.5 L/24 h

Figure 2. Proposed approach to decisions that guide fluid removal and net fluid balance for patients on KRT. The diagram depicts several descriptors of fluid removal and fluid balance used in studies of KRT. This serves to emphasize that the term net UF—which is used in multiple studies of KRT—is substantially different from overall net fluid balance. Exact calculations used in individual studies may vary. Sources of fluid input and output arise from both routine clinical care (non-KRT) and from KRT modalities, including intermittent hemodialysis, prolonged or extended KRT, and continuous KRT such as CVVH and CVVHD. Included is an illustrative example of the concepts of gross UF, net UF, and net UF intensity, as well as cumulative fluid balance in two scenarios: one with low daily non-KRT input and one with high daily non-KRT input. [a]KRT durations are typical examples and assume no interruptions or early cessation of treatment, which may not be the case in clinical practice. [b]Gross UF is the total amount of fluid removed during KRT, not accounting for any KRT-related fluid input. [c]Fluid used to prime the circuit at start of treatment and rinse blood back at end of treatment is often recorded in clinical practice but is frequently ignored in retrospective studies. For continuous modalities, it is assumed that therapy is neither started nor stopped during the 24 hours in question, so no prime or rinse-back fluid is given. [d]Net UF represents the net fluid removed when accounting for KRT fluid input, that is, net UF equals the gross UF minus KRT fluid input. [e]UF Intensity=(Total Net UF for all KRT)/(Days of KRT)/(Admission Weight). For CKRT, number of hours of CKRT is converted into days.[53] For intermittent KRT, each treatment contributes a day of KRT. For patients who receive both, these two are added together. Non-KRT days are not counted. [f]For patients receiving CKRT only, UF intensity can be expressed per hour instead of per day.[53] CKRT, continuous KRT; CVVH, continuous venovenous hemofiltration; CVVHD, continuous venovenous hemodialysis; UF, ultrafiltration.

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unit is per hour, while for participants receiving intermittent KRT, the unit is per day—including only the days on which dialysis is received (therefore ignoring nondialysis days).

In a single-center retrospective study by Murugan *et al.* of critically ill patients with AKI receiving either intermittent KRT or CKRT with pre-KRT positive fluid balance ≥5% above admission body weight, patients who received high-intensity ultrafiltration (defined as an average daily ultrafiltration >25 ml/kg per day) had lower risk-adjusted 1-year mortality compared with patients who received low-intensity ultrafiltration (average daily ultrafiltration <20 ml/kg per day).[53] The association remained consistent in the CKRT-only subgroup, with better survival in patients with ultrafiltration >1 ml/kg per hour compared with ultrafiltration <0.5 ml/kg per hour.[53] Similarly, in a retrospective single-center study of critically ill patients with AKI initiating CKRT, patients who received more intensive ultrafiltration (≥35 ml/kg per day) had higher 30-day survival than those who received low-intensity ultrafiltration (<35 ml/kg per day).[53,54]

By contrast, a separate study by Murugan *et al.* consisting of a secondary analysis of the Randomized Evaluation of Normal versus Augmented Level (RENAL) Replacement Therapy Study found that ultrafiltration >1.75 ml/kg per hour was associated with higher 90-day mortality compared with ultrafiltration <1.01 ml/kg per hour.[55] Using the same ultrafiltration cutoffs in a single-center retrospective cohort, Naorungroj *et al.* demonstrated similar associations with 28-day mortality.[56] Both studies found a dose-dependent relationship between each 0.5 ml/kg per hour higher ultrafiltration and higher mortality.[55,56]

Why are there such different results among these studies? As with all observational data, even with adjustment, these studies are subject to substantial confounding such as from differences in provider practices, severity of illness, indication for KRT, and definition of fluid overload. However, one additional possible explanation is that patients in different

Table 3. Comparison of net fluid balance achieved across studies on net ultrafiltration rate

Study	Metric	Low	Moderate	High
Murugan *et al.* (2018)[53] CKRT subset only	Thresholds for UF rate intensity	≤20 ml/kg per day	20–25 ml/kg per day	>25 ml/kg per day
	Fluid balance before KRT	2.3 L (15.6%)	2.7 L (17.3%)	2.3 L (21.0%)
	UF during KRT (CKRT+intermittent HD)	19.5 L	27.9 L	26.6 L
	Cumulative fluid balance during KRT (excludes UF)	13.5 L	22.0 L	19.0 L
	Cumulative fluid balance during KRT (includes UF)	−6 L (inferred[a])	−5.9 L (inferred[a])	−7.6 L (inferred[a])
	Thresholds for UF rate intensity	<5 ml/kg per hour	0.5–1.0 ml/kg per hour	>1 ml/kg per hour
	Fluid balance before KRT	Unknown	Unknown	Unknown
	Net UF during CKRT	3.4 L	11.6 L	16.2 L
	Cumulative fluid balance during KRT (includes UF)	Unknown	Unknown	Unknown
Tehranian *et al.* (2019)[54]	Thresholds for UF rate intensity	<35 ml/kg per day	No moderate group	≥35 ml/kg per day
	Fluid balance before KRT	4.2 L	—	5.8 L
	UF during CKRT	Unknown	—	Unknown
	Cumulative fluid balance during KRT (includes UF)	Unknown	—	Unknown
Murugan *et al.* (2019)[55]	Thresholds for UF rate intensity	<1.01 ml/kg per hour	1.01–1.75 ml/kg per hour	>1.75 ml/kg per hour
	Fluid balance before CKRT	Unknown	Unknown	Unknown
	UF during CKRT	1.7 L	8.5 L	16.5 L
	Cumulative fluid balance during CKRT (excludes UF)	4.6 L	8.5 L	11.1 L
	Cumulative fluid balance during CKRT (includes UF)	+2.3 L	−0.4 L	−3.6 L
Naorungroj *et al.* (2021)[56]	Thresholds for UF rate intensity	<1.01 ml/kg per hour	1.01–1.75 ml/kg per hour	>1.75 ml/kg per hour
	Fluid balance before KRT	0.22 L	0.31 L	0.68 L
	UF during CKRT	1.0 L	3.6 L	5.3 L
	Cumulative fluid balance during KRT (includes UF)	+0.53 L	−0.66 L	−1.75 L

This table provides a detailed comparison of the net fluid balance within each of the net ultrafiltration groups (low, moderate, and high) across the four studies detailed in Table 2. Net fluid balance before initiation of KRT and during KRT is listed for each category of ultrafiltration intensity, when available. CKRT, continuous KRT; UF, ultrafiltration; HD, hemodialysis.

[a]An inferred value rather than a reported value based on the following two assumptions for comparison purposes only. If fluid balance during KRT is not reported, then the net fluid balance after KRT including UF, the difference between the cumulative fluid balance during KRT (excluding UF), and the UF during KRT was used to estimate the median cumulative fluid balance during KRT (including UF). Note that while the studies refer to a net UF to account for the administration of intravenous fluids needed to complete KRT (in the case of these studies, this consisted of replacement fluid during hemofiltration), to avoid confusion all fluid removal achieved using KRT is referred to simply as UF.

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studies may not have been in the same fluid management phase. In studies that found high ultrafiltration rate to be associated with lower mortality,[53,54] patients had significant positive fluid balance at KRT initiation (Table 3). By contrast, participants in Naorungroj *et al.*[56]—in whom high ultrafiltration rate was associated with higher mortality—had only minimally positive fluid balance at baseline. In addition, this study used only the ultrafiltration rate during the first 48 hours of KRT the analysis, reasoning that this is "a time where illness severity may be most likely to be either positively or negatively affected by [ultrafiltration] management."[56]

Ultrafiltration Rate versus Net Fluid Balance

Both the ROS-D model and typical clinical practice focus on net fluid balance rather than fluid removal alone. Just as it is difficult to infer net fluid balance during diuresis from urine output alone, net fluid balance in patients receiving KRT cannot be extrapolated from only the daily ultrafiltration (Figure 2). A quick glance at the four cohort studies in Table 3 shows that three of the studies seem to have different amounts of cumulative fluid balance during KRT, and the fourth does not report fluid balance during KRT at all.[54] Moreover, the relationships among ultrafiltration rate, net fluid balance during KRT, and mortality differ among the studies. In the two studies showing higher mortality associated with higher ultrafiltration rate, the low-intensity groups had a net positive median fluid balance during KRT, and the high-intensity groups had a net negative median balance.[55,56] By contrast, in the single-center study by Murugan *et al.*[53]—which found lower mortality with high ultrafiltration rate—all groups seemed to have a net negative median balance. This is additional evidence that the latter study is drawn from a different patient population than the former two. Focusing on ultrafiltration rate alone may mask this important observation.

Ultrafiltration rate is therefore a problematic stand-alone metric for either clinical investigation or clinical management at the bedside, especially for critically ill patients who have widely varying fluid intake. The same ultrafiltration rate may lead to either volume overload or volume depletion if there are different amounts of fluid input and/or non-KRT fluid loss (Figure 2). Even in the outpatient setting, implementing ultrafiltration rate thresholds without consideration of overall volume status can lead to unintended fluid-related weight gain and failure to achieve target weights.[57]

Net fluid balance is therefore a more clinically relevant target during KRT. A recent retrospective study of critically ill patients with AKI receiving CKRT found that achieving a greater reduction in cumulative fluid balance was associated with lower ICU and hospital mortality.[58] There are several other important findings from this study. First, fluid balance before CKRT initiation was not associated with mortality after adjustment for severity of illness and need for vasopressor support, suggesting that confounding factors are contributing to the higher mortality in unadjusted analysis of baseline fluid overload. Second, while the achievement of a lower cumulative fluid balance during CKRT was independently associated with lower mortality, the duration of time needed to reach it was not. This raises the possibility that the rate of decongestion CKRT is less important than achievement of decongestion itself. Third, the number of days when a fluid balance goal was set correlated positively with the likelihood of achieving a lower cumulative fluid balance during CKRT, further supporting the importance of fluid balance goals to guide management. The relevance of achieving these goals was emphasized in a recent study showing that a larger gap between prescribed and achieved fluid balance was independently associated with higher mortality in a cohort of critically ill patients receiving CKRT.[59] Of note, while low ultrafiltration rate was also associated with higher mortality, this association was no longer present after adjustment for the gap between prescribed and achieved fluid balance as well as other clinical parameters. This further suggests that targets based on fluid balance may be preferable to those based on ultrafiltration rate alone.

Of course, as with all observational studies, RCTs will be needed to confirm the benefit of achieving net fluid balance on clinically relevant outcomes.

Defining Fluid Overload versus Fluid Intolerance

Many observational studies have defined fluid overload based on percent net fluid gain divided by weight on admission, often using an arbitrary cutoff such as a >10% increase to define fluid overload.[50,60–62] By this definition, fluid overload is clearly associated with higher mortality, AKI, and other negative outcomes.[50,60–62] However, this metric is limited by confounding given that fluid gain is associated with severity of illness and degree of volume depletion on admission. In addition, there are practical challenges to measuring net fluid balance precisely. Thus, the presence of fluid overload defined purely by net positive fluid balance compared with admission weight is not likely to justify fluid removal in an individual patient.

The degree of net positive fluid balance must be placed in context of both evidence of fluid responsiveness and signs of fluid toxicity. It is important to point out that the presence of fluid responsiveness does not preclude fluid toxicity. Even when cardiac output is augmented, additional fluid administration can still have negative consequences such as worsening hypoxemia or increasing intra-abdominal pressure. The degree to which a patient can receive fluid without developing toxicity has been defined as fluid tolerance.[63,64] When clinicians at the bedside discuss volume overload, they are often referring to evidence of fluid toxicity/intolerance, rather than merely net positive fluid balance.

Particularly in the critically ill population, multiple factors—including cardiopulmonary function and the presence of pathologic capillary leak—affect the balance between fluid responsiveness and fluid tolerance.[65] Point-of-care ultrasound has emerged as an important bedside tool to rapidly and noninvasively assess parameters associated with both fluid responsiveness and fluid intolerance (*e.g.*, repeated presence of B lines on lung ultrasonography or evidence of right ventricular overload on echocardiography).[20,66–68] As these techniques continue to mature, they will likely need to be combined with the metric of net fluid gain to guide optimal management.

Avoiding Hypoperfusion due to Fluid Removal Using KRT

Just as the presence of fluid responsiveness may not rule out fluid toxicity, the toxicity from fluid does not ensure that

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its removal will be well tolerated. As recent reviews have described,[69,70] classic strategies to mitigate hemodynamic instability—such as higher dialysate sodium concentration, ultrafiltration profiling, isolated ultrafiltration, and cooled dialysate—have limited data that are largely extrapolated from the outpatient setting. Among the various strategies, cool dialysate temperature has the best evidence base and is already widely used.

Regardless, the most important element in avoiding ischemic injury due to fluid removal during KRT is knowing when to stop removing fluid. Many clinicians use a decline in MAP or escalating pressors as triggers to decrease fluid removal. A MAP ≥65 mm Hg has been suggested as a target in most forms of shock.[71,72] With a more proactive approach, it may be possible to predict intradialytic hypotension during ultrafiltration using bedside maneuvers normally used to predict fluid responsiveness.[73–75]

Unfortunately, BP is a crude measure of hemodynamic status and often an inadequate marker for adequate organ perfusion. Myocardial stunning has been demonstrated during ultrafiltration—regardless of BP changes—in patients with kidney failure undergoing routine intermittent hemodialysis (HD), patients starting intermittent HD for AKI, and even critically ill patients within hours of initiating CKRT.[76–78] Whether these observations are due to dialysis, ultrafiltration, or other factors pertaining to critical illness remains unclear.

Tissue perfusion has correlated better with microcirculatory alterations than with changes in systemic BP.[79,80] Near infrared spectroscopy is a growing area of research to noninvasively measure changes in regional microcirculation, particularly in cerebral blood flow and oxygenation during KRT.[81–83] However, it is not generally available for clinical use.

Continuous blood volume monitoring is a technique that is directly integrated into several currently available intermittent HD machines. By optically measuring changes in hematocrit in real-time, relative changes in blood volume can be measured, and the plasma refill rate can be estimated.[84] Unfortunately, studies of this technology in the outpatient setting have had mixed results.[85–87] One randomized trial using it to guide ultrafiltration rate during intermittent HD in critically ill patients showed no difference in hemodynamics or intradialytic complications.[88] While newer studies suggest novel methods to use blood volume monitoring to inform decisions regarding ultrafiltration,[89–92] these are at a preliminary phase and have only been studied in outpatients. It therefore remains unclear whether this technique will prove useful in the critical care setting.

Conclusion

Current evidence and technologies are insufficient to provide clarity regarding optimal fluid management strategies using KRT in the critically ill. However, we believe there are reasonable inferences that can be drawn from the existing literature to guide both current management and future investigation.

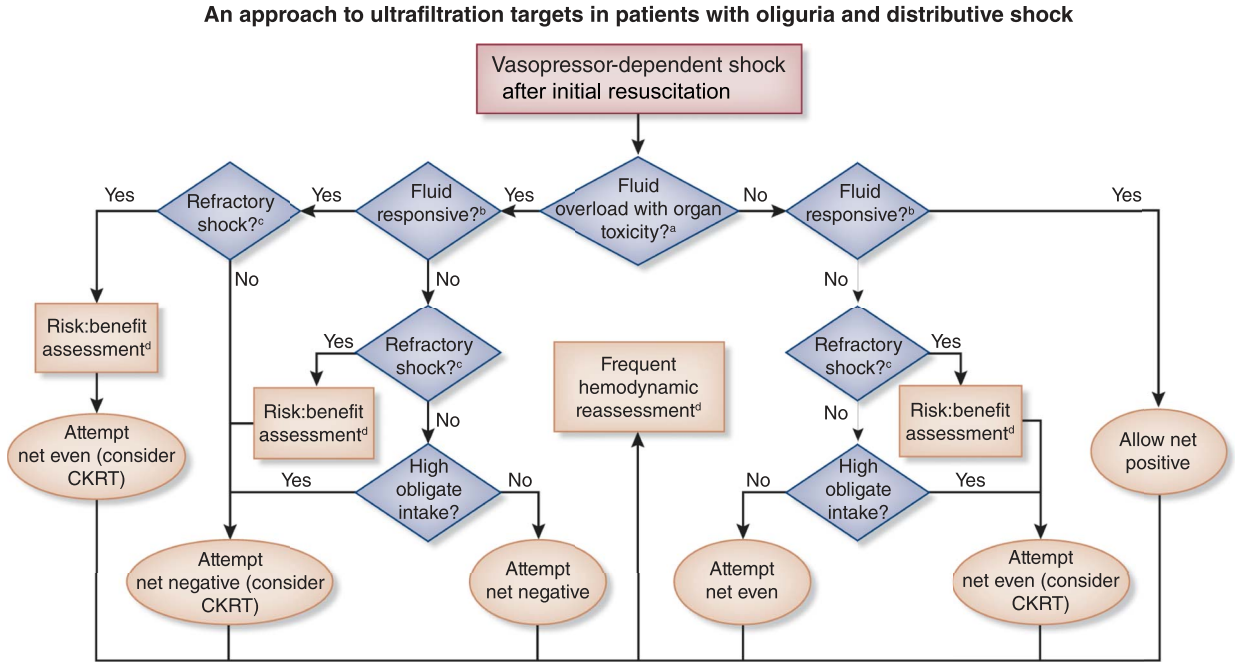

Figure 3. An approach to ultrafiltration targets in patients with oliguria and distributive shock. [a]Examples of fluid overload with organ toxicity include the following: pulmonary edema, right ventricular volume overload, elevated intra-abdominal pressure, and elevated central venous pressure with decreased organ perfusion pressures. [b]Fluid responsiveness is commonly defined as a 10%–15% increase in cardiac output after an intravenous fluid bolus and may be predicted with provocative maneuvers.[24,25] [c]There is no consensus definition for refractory shock. Examples include the following: high doses of an intravenous vasoactive medication (*e.g.*, >0.2 μg/kg per minute of norepinephrine or equivalent), need for multiple vasoactive medications, or adjunctive glucocorticoid therapy. [d]As part of the frequent hemodynamic reassessment, discussions with the intensive care unit team should involve decisions on the priority of fluid removal, limits of vasopressor titration, and ultimately optimal kidney replacement modality to achieve fluid targets.

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First, both clinical management and research protocols should focus, when possible, on net fluid balance rather than simply the ultrafiltration rate. While the latter is easier to measure, the former is more clinically relevant. Consequently, we prescribe fluid removal on CKRT at our institution as a net 24-hour fluid balance goal rather than an absolute ultrafiltration rate. This is resource-intensive for the nursing staff because it requires hourly assessments of non-KRT fluid balance and frequent adjustments of ultrafiltration rate. However, we feel this approach increases the likelihood that volume management goals will be achieved while also allowing CKRT fluid goals to be readily interpretable by the ICU team.

Second, fixed numeric guidelines of either ultrafiltration rate or net fluid balance are unlikely to be adequate given the dynamic needs of critically ill patients managed with KRT. Repeated assessments of fluid responsiveness and fluid toxicity are needed to guide fluid balance and ultrafiltration goals. Feasible protocols based on physiologic rationales that also leverage available assessment methods (Figure 3) are needed both as a starting point for current clinical management and to design trials to test effect on patient-centered outcomes.

Third, the focus of volume management using KRT should not be limited to the earliest stages of critical care. The stabilization and de-escalation phases may be particularly suited for future trials. For patients on CKRT, the transition to intermittent therapy can be a vulnerable period and may provide a useful study target. In one recent study of patients transitioning from CKRT, intra-dialytic hypotension occurred during 50% of first intermittent HD treatments and was independently associated with mortality.[93] In addition, the critical care goals during later phases of management—such as durable liberation from mechanical ventilation and intravenous vasopressors—may serve as useful surrogate outcomes for smaller preliminary trials that would not be powered to examine mortality.[94]

Awaiting more robust evidence, we suggest that such critical care goals should still inform our decisions about volume removal targets and the means to achieve them. Should an edematous patient currently on CKRT be switched to intermittent HD as soon as intravenous pressors are discontinued or should CKRT be continued until there is minimal evidence of pulmonary edema? While the answer remains uncertain, merely assessing whether the patient is likely to tolerate intermittent HD seems unlikely to be sufficient for this decision. Comprehensive assessment of factors such as degree of volume overload, daily fluid intake, ventricular function, respiratory status, and functional goals should inform the optimal approach.

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